REMARKS

Status of the Claims and Support for the Claim Amendments

Applicants have amended claim 11 to better capture the envisioned commercial embodiments. The specification and originally filed claims fully support the claim amendments. Applicants assert that the elements in present claim 11 were in previously presented versions of the claim and thus, current claim 11 should have been previously searched. Applicants assert, therefore, that the new claims do not require a new search and thus can be entered into the application.

The Claimed Invention is Not Obvious

Teichberg, Aminova and Lu

The Office Action rejected claims 11, 13-15, 24-38 as allegedly obvious in view of Teichberg, *et al.* (U.S. Pre-grant Publication No. 2006/0024284) ("Teichberg"), Aminova *et al.* (Aminova, L.R., *et al., J. Biol. Chem.*, 280(5):3996-4003 (2005)) ("Aminova") and Lu *et al.* (Lu, H., *et al., J. Biol. Chem.*, 277(26):23111-23115 (2002)) ("Lu"). Applicants respectfully disagree.

As an initial matter, Applicants note that the Office Action states that "Teichberg fails to directly disclose the relationship between the glutamate concentration and HIF-1 mediated gene expression." *Final Office Action of 9 September 2009*, page 4. The Office Action then attempts to tie in glutamate levels with HIF-1 levels by citing Aminova. Applicants note that Aminova does not qualify as prior art to the present application. Aminova has a publication date of 4 February 2005, and, according to the journal's website, was first published on-line on 22 November 2004. The present application was filed as an international PCT application on 8 November 2004 and claims priority to U.S. Provisional Application 60/517,918, filed 7 November 2003. Both the priority date and the PCT filing date of the present application pre-date the publication date of Aminova. Accordingly, Aminova does not qualify as prior art to the present application. The Office's reliance on Aminova is improper.

Moreover, Aminova does not even teach or stand for the proposition that the Office is asserting. In spite of the previous response to Office Action in which Applicants pointed out that Aminova is not prior art, the Office continues to assert Aminova and states that "Aminova teaches that HIF levels are higher at reduced glutamate levels (see Aminova, figure 5c)." This previous assertion is wrong. Figure 5c shows that cells die as the concentration of glutamate in increased. In Figure 5c of Aminova, the y-axis is

labeled "% cell viability" and the x-axis is labeled "glutamate." Thus Figure 5c is a dose response curve, where the "response" is cell death. Figure 5c of Aminova, in no way, shows or even suggests that HIF levels go down in response to glutamate. The key in Figure 5c that names "siHIF", which is presumably where the Examiner focused his attention, is a curve for a cell population that constitutively expresses HIF. Figure 5a and the "Experimental Procedures" sections confirms this when it discloses that HT22 cells were infected with retroviral vectors containing HIF. As the Examiner should know, infection of cells with a retrovirus would indicate that HIF levels are constitutively and constantly expressed. Thus Figure 5c does not disclose that HIF levels are higher at reduced glutamate levels. Thus, even if Aminova is considered prior art to the present application, which it most certainly is not, Aminova does nothing to associate HIF levels and glutamate.

After Aminova is removed as a reference, Applicants assert that the Office cannot sustain the obviousness rejection. First, the collection of remaining references (Teichberg and Lu) fails to teach each and every element of the claimed invention; second, the Office has not identified any type of motivation that one of skill in the art would have in applying the teachings of Teichberg and Lu to subjects in need of neovascularization therapy. Finally, the Office has not identified any reasonable expectation of success or predictability in applying the teachings of Teichberg and Lu to promote neovascularization in subjects in need of such treatment.

The claims recite a method of promoting neovascularization in a subject comprising administering a composition comprising an amount of at least one 2-oxoacid to a subject in need of such treatment. The remaining cited art (Teichberg and Lu), however, does not teach or suggest identifying a subject in need of neovascularization therapy. At best, Teichberg discloses reducing glutamate levels in the central nervous system (see ¶0001 of Teichberg). Teichberg does not disclose or suggest that glutamate levels are associated with either levels of HIF-1 or with neovascularization activity. More importantly, "glutamate" is not a claim element and "reducing glutamate levels" is also not a claim element. In other words, one of skill in the art would recognize that Teichberg is entirely irrelevant to the currently claimed invention.

The Office Action also states that "Aminova provides evidence that as glutamate levels decrease, HIF increases. Therefore, the patient in Teichberg whose glutamate levels are decreased would necessarily show increased HIF-1 expression, particularly in view of the evidence provided by Aminova."

Apparently, the Office is stating that a patient administered the compounds of Teichberg will necessarily undergo neovascularization, based on evidence from Aminova. Even if true, however, this statement fails to account for all claim elements, which include specific selection of patient population in which neovascularization is desired. The cited art, exclusive of Aminova, *must* teach or suggest a selection of a patient population in which neovascularization is required. Moreover, the cited art cannot, somehow, inherently teach the purposeful selection of a patient population needing neovascularization therapy.

Teichberg discloses a laundry list of agents that are effective to reduce extracellular brain glutamate levels that encompasses hundreds if not thousands of different compounds, including NAD^+ (*see* ¶0025 of Teichberg). Aminova mentions the word "glutamate" and "HIF-1." From the list in Teichberg and the mention of two words in Aminova, the Office has done nothing but pick and choose select words from references, one of which is not even prior art to the current application and reached a "conclusion" of obviousness. Applicants assert that the Examiner must view the reference as one skilled in the art would view the reference and take the reference as a whole, without the guidance of the present application. The Examiner can not pick out specific, isolated words from a reference and simply assert that the reference "teaches" these concepts. Such picking and choosing is "illogical and inappropriate" when determining obviousness. Indeed,

> rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'

In re Rouffet 149 F.3d 1350, 1357, 47 U.S.P.Q. 2d 1453, 1457 (quoting *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d (BNA) 1551, 1554 (Fed. Cir. 1996)).

The Office Action concludes by stating that it would have been obvious "to utilize the composition of Teichberg in amounts significant enough to induce HIF-1 mediated gene expression since Teichberg teaches a composition for the reduction of glutamate, and Aminova teaches a relation between the concentrations of glutamate and HIF." *Final Office Action of 9 September 2009*, page 4. Further, [t]here would be a reasonable expectation that Teichberg would use an effective amount of

glutamate to induce HIF-1 mediated gene expression based on the evidence shown in figure 5c of Aminova wherein the relationship is identified." *Id.*

It seems clear that the Office is relying on Aminova to demonstrate the requisite motivation and reasonable expectation of success. But this motivation and expectation of success are misplaced in Aminova. As discussed herein, Aminova is not prior art to the present application, so the Office cannot rely upon Aminova for any aspect of establishing a *prima facie* obviousness rejection. Moreover, even if the Office were to continue to improperly rely upon Aminova, this reference does not teach the relationship that the Office is alleging. Aminova simply shows that increasing glutamate in cell culture kills every cell type tested (each cell type had an identically shaped dose response curve). Thus, Aminova, at most teaches that cell viability decreases with increasing glutamate concentrations. But Aminova, in no way, shows that HIF levels are somehow higher at reduced glutamate levels. Aminova would thus fail to provide any reasonable expectation of success to one of skill in the art.

Finally, Applicants note that the Office incorrectly ties in neovascularization with coronary bypass surgery. "[I]t has been established that the composition is taught by Teichberg to be utilized on patient [*sic*] who are having coronary bypass surgery, which, like any major surgery, would require wound healing." *Final Office Action of 9 September 2009*, page 4. Even if the Office persists in maintaining the improper obviousness rejection of the claims, Applicants note that the amended claims not related in any way to coronary bypass surgery. Applicants assert, therefore, that the cited art (Teichberh and Lu) fail to render obvious methods wherein the patient population has any of the claimed conditions.

For the foregoing reasons, Applicants submit that the pending claims are not obvious and that the obviousness rejection be withdrawn.

CONCLUSION

Applicants have amended claim 11 to better capture the envisioned commercial embodiments. Applicants assert that the specification and originally filed claims fully support the amended claims. Applicants also assert that the claims are not obvious in view of the cited art (Teichberg and Lu).

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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